Incomplete DNA methylation underlies a transcriptional memory of somatic cells in human iPS cells.

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Public Summary:
Adult specialized cells can be turned into induced pluripotent stem cells (iPS cells) by activation of key genes. Most of the experiments showing that this is possible have been done with skin fibroblasts. We compared the process of generating iPS cells made from 3 very distinct cell types. We found that iPS cells "remember" their cell of origin, that is, they retain a residual memory of gene activity from the original cells. We describe the genetic underpinnings of this phenomenon and implicate a key chemical modification of DNA, DNA methylation, in this process.

Scientific Abstract:
Human induced pluripotent stem (iPS) cells are remarkably similar to embryonic stem (ES) cells, but recent reports indicate that there may be important differences between them. We carried out a systematic comparison of human iPS cells generated from hepatocytes (representative of endoderm), skin fibroblasts (mesoderm) and melanocytes (ectoderm). All low-passage iPS cells analysed retain a transcriptional memory of the original cells. The persistent expression of somatic genes can be partially explained by incomplete promoter DNA methylation. This epigenetic mechanism underlies a robust form of memory that can be found in iPS cells generated by multiple laboratories using different methods, including RNA transfection. Incompletely silenced genes tend to be isolated from other genes that are repressed during reprogramming, indicating that recruitment of the silencing machinery may be inefficient at isolated genes. Knockdown of the incompletely reprogrammed gene C9orf64 (chromosome 9 open reading frame 64) reduces the efficiency of human iPS cell generation, indicating that somatic memory genes may be functionally relevant during reprogramming.